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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C12N 15/00, C07H 21/04, 21/02, C07K 1/00, C12P 21/06, A01N 63/00, 43/04, A61K 45/00, 39/00

A1

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: INHIBITION OF THE MHC CLASS II ANTIGEN PRESENTATION PATHWAY AND PRESENTATION TO CD4+ CELLS

(57) Abstract

The human cytomegalovirus (HCMV) protein, that was previously shown to block the MHC class I antigen presentation pathway, has been shown herein to block the MHC class II pathway. This is surprising because the class I and class II proteins are not homologous. US2 caused degradation of class II-alpha proteins and also class II-DM-alpha, part of an enzymatic complex required for loading of antigenic peptides. In this way, US2 has a double inhibitory effect on the MHC class II pathway. US2 expression in cells effectively blocked presentation of antigens to CD4+ T lymphocytes. US2, or soluble variants thereof, can be used to reduce inappropriate immune responses directed to vectors, or expressed transgenes. In addition, such molecules can be used to block immunity to transplanted cells or organs or in autoimmune diseases.

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/02740

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/320.1, 69.1; 536/23.1, 24.1; 424/93.21, 184.1; 530/350; 514/44;

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN,
SEARCH TERMS: HCMV US2 OR USII, US2 PROTEIN, MHC2 OR MHCII MOLECULES,

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | Database Swissprot 38 on gencore, No. P09713, Weston, K. et al. 'Sequence of the short unique region, short repeats, and part of the long repeats of human Cytomegalovirus,' J. Mol. Biol. 1986, Vol. 192 pages 177-208, see entire document. | 6-7, 23 |
| X | Database A-geneseq 36 on gencore 4.5, No. R34706, Glick, D.L. et al. 'Purified DNA encoding eukaryotic nad cyclase-useful for prodn. Of cyclic adenosine di: phosphate ribose from NAD,' US 5202426 A, 13 April 1993, see cols 15-18. | 23 |
| Y | Database Pir-62 on gencore 4.5, No. E26078, SO9916, Weston, R. et al. 'Sequence of the short unique region, short repeats, and part of the long repeat'. J. Mol. Biol. 1986, 192, pages 177-208, see entire document. | 25 |

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

| | | | |
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| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date of the actual completion of the international search<br>21 APRIL 2000 | Date of mailing of the international search report<br>30 MAY 2000 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>YVETTE CONNELL<br>Telephone No. (703) 308-0196 |

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/02740

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 5,843,458 A (JONES et al.) 01 December 1998 (01/12/98), see entire document. | 1-38 |
| A | WO 97/32605 A1 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 12 September 1997(12/09/97), see entire document. | 1-38 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/02740

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C12N 15/00; C07H 21/04, 21/02; C07K 1/00; C12P 21/06; A01N 63/00, 43/04; A61K 45/00, 39/00;

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/320.1, 69.1; 536/23.1, 24.1; 424/93.21, 184.1; 530/350; 514/44;

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

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United States Patent and Trademark Office
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in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>04 October 2000 (04.10.00) | |
| **International application No.**<br>PCT/US00/02740 | **Applicant's or agent's file reference**<br>899-54203 |
| **International filing date** (day/month/year)<br>02 February 2000 (02.02.00) | **Priority date** (day/month/year)<br>02 February 1999 (02.02.99) |
| **Applicant**<br>JOHNSON, David, C. et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

24 August 2000 (24.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
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09/890806

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PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

**(PCT Article 36 and Rule 70)**

| Applicant's or agent's file reference 899-54203 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
|---|---|---|
| International application No. PCT/US00/02740 | International filing date *(day/month/year)* 02 FEBRUARY 2000 | Priority date *(day/month/year)* 02 FEBRUARY 1999 |
| International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet. | | |
| Applicant OREGON HEALTH SCIENCES UNIVERSITY | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 24 AUGUST 2000 | 22 OCTOBER 2001 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>Dorothea Lawrence for<br>ANNE MARIE BECKERLEG<br>Telephone No. (703) 308-0196 |

Form PCT/IPEA/409 (cover sheet) (July 1998) ★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/02740

## I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-31, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the claims:
pages 32-35, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the drawings:
pages 1-8, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the sequence listing part of the description:
pages 1-5, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/fig NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/02740

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 5-7, 9, 14, 16-38 | YES |
| | Claims | 1-4, 8, 10-13, 15 | NO |
| Inventive Step (IS) | Claims | 5-7, 9, 14, 16-38 | YES |
| | Claims | 1-4, 8, 10-13, 15 | NO |
| Industrial Applicability (IA) | Claims | 1-38 | YES |
| | Claims | NONE | NO |

2. citations and explanations (Rule 70.7)

Claims 1-4, 8, 10-13, and 15 lack novelty under PCT Article 33(2) as being anticipated by WO 97/32605 12 September 1997, hereafter referred to as Ploegh et al. The claims recite vectors encoding HCMV US2 and methods of inhibiting the recognition of cellular tissue or the methods of preventing or treating autoimmune disease by administering an effect amount of said vector. The claims further recite wherein the vector is a viral vector and and wherein the US2 has not been mutated to recognize MHC class II.

Ploegh et al. teaches vectors, including adenoviral or vaccinia viral vectors, encoding wild type HCMV US2, and the administration of said vectors to mammals to prevent autoimmune disease (Ploegh et al., see pages 8-10, especially page 10, and page 27, claims 25-28). It is noted that while Ploegh et al. does not specifically teach that US2 has MHC class II inhibiting activity, such activity is inherent to the wild type US2 protein. Thus, by teaching all the limitations of the claims, P loegh et al. anticipates the instant invention.

Claims 1-4, 8, and 10-11 lack novelty under PCT Article 33(2) as being anticipated by Machold, R.P. et al., J. Exp. Med. , January 20, 1997, Vol. 185, pages 363-366. The claims recite vectors encoding HCMV US2 and methods of inhibiting the recognition of cellular tissue by CD4+ and CD8+ T cells by administering an effect amount of said vector. The claims further recite wherein the vector is a viral vector and and wherein the US2 has not been mutated to recognize MHC class II.

Machold et al. teaches vaccinia virus vectors encoding wild type HCMV US2 and the transfection of mammalian cells with the vaccinia virus resulting in the degradation of MHC class I molecules which in turn inhibits recognition of the transfected cells by T cells (Machold et al., page 364, Figure 1, and page 366). It is noted that while Machold et al. does not specifically teach that US2 has MHC class II inhibiting activity, such activity is inherent to the wild type US2 protein. Thus, by teaching all the limitations of the claims, Machold et al. anticipates the instant invention.

(Continued on Supplemental Sheet.)

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII



CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C12N 15/00; C07H 21/04, 21/02; C07K 1/00; C12P 21/06; A01N 63/00, 43/04; A61K 45/00, 39/00; and US Cl.: 435/320.1, 69.1; 536/23.1, 24.1; 424/93.21, 184.1; 530/350; 514/44;

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Claims 5, 9, 14, and 16-38 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or f airly suggest the administration of HCMV US2 protein to inhibit cellular immune responses or treat disease, or teach a soluble US2 variant.

Claims 1-38 meet the criteria set out in PCT Article 33(4) for industrial applicability.

---------- NEW CITATIONS ----------

MACHOLD. R. P. et al. "The HCMV gene products US11 and US2 differ in their ability to attack allelic forms of murine major histocompatibility complex (MHC) class I heavy chains." J. Exp. Med. January 20, 1997. Vol. 185. pages 363-366, see especially page 364.